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PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
FALK, ANNE MARIE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,384	ZOGHBI ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13-15,17,18,20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) *4,5,7-11,13-15,17,18,20,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The responses filed August 16, 2004 and December 6, 2004 have been entered. The remarks filed February 25, 2004 (herein after referred to as "the response") are considered herein. Claim 21 has been cancelled.

Accordingly, Claims 1, 3-11, 13-15, 17, 18, 20, and 22-25 remain pending.

Claims 4, 5, 7-11, 13-15, 17, 18, 20, 22, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicants timely traversed the restriction requirement in the response filed 3/18/03.

Accordingly, Claims 1, 3, 6, 24, and 25 are examined herein.

The objection to the drawings is withdrawn in view of the drawing correction filed February 25, 2004 and the amendment filed December 6, 2004.

The objection to Claims 21 and 24 is withdrawn in view of the cancellation of Claim 21 and the amendment of Claim 24.

The double patenting warning is withdrawn in view of the cancellation of Claim 21.

The rejection of Claims 1, 3, and 6 under 35 U.S.C. 102(a) is withdrawn in view of Applicants' arguments at pages 16-17 of the response. Applicants assert that the reference does not provide an enabling disclosure for treating the neurodegenerative disease transmissible spongiform encephalopathy by administering a chaperone. Applicants assert that undue experimentation would have been required for one skilled in the art to perform the method taught by Weiss et al. The Examiner agrees that, for

many of the same reasons discussed below with regard to enablement of the instant invention, undue experimentation would have been required to carry out the method of Weiss et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1, 3, 6, 24, and 25 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons set forth in the Office Action mailed 10/22/03.. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The chaperone, nucleic acid, or non-protein, non-nucleic acid compound to be administered to a mammal is an essential element of the claimed invention. However, the specification only describes a single species of therapeutic compound, namely HDJ-2/HSDJ, that could be used in the claimed methods. The specification does not describe any compound that could be used in practicing the method of the invention for treatment of Alzheimer's disease, Parkinson's disease, prion diseases, or any other neurodegenerative disease other than SCA1. In the absence of a written description of the therapeutic compounds, the claimed methods lack written description for the complete genus because the therapeutic compound is an essential element of the claimed method. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, no compounds other than HDJ-2/HSDJ are described. Next then, it is determined whether a representative number of species have been sufficiently

described by other relevant identifying characteristics. In this case, no particular identifying characteristics are described for other therapeutic compounds. For example, the specification does not provide a written description of a chaperone that would be effective in the treatment of Alzheimer's disease or Parkinson's disease. Thus, the specification does not describe the genus of therapeutic compounds to be used in the claimed methods. This limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the genus of therapeutic compounds for use in the claimed methods. Thus, it is concluded that the written description requirement is not satisfied for methods of using the genus of compounds recited in the claims.

At page 8 of the response, Applicants assert that the specification describes Hsp60, Hsp40, and Hsp70 as being compounds that could be used to treat neurodegenerative diseases. Applicants further assert that Hsp70 is "taught to be part of a family of chaperones" (page 8 of the response). Applicants conclude that, because members of families are mentioned, the specification describes the families, and thus a large number of chaperones. However, the Examiner does not agree that the mention of a few family members provides description for the entire families. Applicants are reminded that the Hsp70 family of proteins includes Hsp70 (in the cytosol and mitochondrial matrix), Bip (in the endoplasmic reticulum), and DnaK (in bacteria). However, the specification does not describe the Hsp70 family, but rather only describes Hsp70 itself. While the specification indicates on page 9, line 28 that "Hsp60, Hsp40, and Hsp70 are examples of such proteins," referring to chaperones in general, the specification does not describe the entire families of which these exemplary proteins are members, such as the entire Hsp70 family, as being chaperones of the invention. Thus, while the specification describes a few species of chaperones that are asserted to be useful in the methods of the invention, the written description of compounds that can be used in the claimed methods is quite limited.

Furthermore, it is noted that the claims cover the use of **any compound** that "increases the effective concentration of a chaperone in the neurological system" (Claim 6), any chaperone compound which suppresses ataxin-1 aggregation (Claim 24), and any "compound preparation which suppresses ataxin-1 aggregation" (Claim 25). Thus, the claims cover the use of non-protein, non-nucleic acid compounds as well as the use of chaperone proteins themselves and nucleic acids encoding chaperones. However, the specification does not describe a single non-protein, non-nucleic acid compound that "increases the effective concentration of a chaperone in the neurological system" or "suppresses ataxin-1 aggregation." The only compounds that the specification describes as compounds that would increase the effective concentration of a chaperone in the neurological system are the chaperones themselves and nucleic acids encoding the chaperones.

It is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991). The Court went on to point out that "[i]t is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016, 1021 (CAFC 1991). Thus, it is not sufficient to describe a compound solely by its biological activity, such as a compound that "increases the effective concentration of a chaperone in the neurological system" (Claim 6) or a compound that "suppresses ataxin-1 aggregation" (Claim 25).

Where the claims are limited to directly injecting a chaperone into a mammal (Claim 3), it is noted that the term "chaperone" covers a very large class of proteins, but the specification does not disclose a sufficient number of species within the very large genus that have the desired activity of treating the wide variety of neurodegenerative diseases covered by the claims.

At page 9, paragraph 2 of the response, Applicants assert that the specification does describe compounds that could be used to treat Alzheimer's disease or Parkinson's disease because "a chaperone that modifies the protein aggregation behavior of a protein involved in one of these disorders is a candidate for treatment of that disorder." However, the specification does not describe, for example, "a chaperone that modifies the protein aggregation behavior of a protein involved in" Alzheimer's disease, nor does the specification describe "a chaperone that modifies the protein aggregation behavior of a protein involved in" Parkinson's disease. Claim 24 now recites "a chaperone compound which suppresses ataxin-1 aggregation" and Claim 25 now recites "a compound preparation which suppresses ataxin-1 aggregation." Both claims cover the treatment of any neurodegenerative disease whatsoever, but the specification does not describe the genus of compounds that suppress ataxin-1 aggregation and treat Alzheimer's disease, Parkinson's disease, etc. The specification only describes a single chaperone that has the activity of suppressing ataxin-1 aggregation, *i.e.* the HDJ-2/HSDJ chaperone protein. The claims cover any chaperone with this activity as well as any other compound with this activity, but the specification does not describe other compounds with this activity.

The Guidelines for Written Description state that "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (MPEP §2163(3)(a)(ii)). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice ..., reduction to drawings ..., or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)). In the instant case, the claims cover the use of **any compound** that has the desired activity, but the specification only describes a single chaperone protein that suppresses ataxin-1 aggregation.

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 97 F.2d 623, 38 USPQ 189 (CCPA 1938); *In re Wahlforss et al.*, 117 F.2d 270, 48 USPQ 397 (CCPA). The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary. *In re Shokal et al.*, 113 USPQ 283, 285 (CCPA 1957). In the instant case, the genus of "compounds" as recited in certain claims is very large, whereas compounds that have the desired activity would represent a very small group, although diverse classes of compounds could potentially have the desired activity. In the instant case, only a single chaperone protein having the desired activity is described.

At page 9, paragraph 3 of the response, Applicants assert that they have described a structure-function correlation between the conserved domains of HDJ-2/HSDJ and its chaperone activity. However, the claims are not limited to chaperones having any particular structure, so it is unclear why Applicants are arguing the structure-function correlation. While the claims cover the use of chaperones that have the conserved domains, it also covers the use of chaperones that do not. The claims are directed to the use of any chaperone whatsoever. The specification does not provide a written description of compounds that have the desired activity, beyond the single disclosed species. The claims cover the use of diverse compounds that have no structural relationship at all, as well as compounds that have no functional relationship (as for example, transcription factors that may upregulate expression of a chaperone vs. a small organic compound that suppresses protein aggregation through a receptor-mediated process).

The Guidelines for Written Description specifically state that "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" (Federal Register, Vol. 66, No. 4, page 1105, column 1).

Thus, it is maintained that the written description requirement is not satisfied for methods of using the genus of compounds recited in the claims.

Enablement

Claims 1, 3, 6, 24, and 25 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The following factors have been considered.

Nature of the invention and scope of the claims. The claims are drawn to a method of treating neurodegenerative disease in a mammal. Claims 1 and 3 are directed to introducing a therapeutically effective amount of a chaperone into the neurological system of a mammal. Claim 6 is directed to introducing a therapeutically effective amount of a compound that increases the effective concentration of a chaperone in the neurological system of a mammal. Claims 21, 24, and 25 are directed to introducing a

therapeutically effective amount of a compound which suppresses ataxin-1 aggregation into the neurological system of a mammal. The claims encompass protein therapy, gene therapy, and non-protein, non-nucleic acid compound therapy. Thus, the claims are very broad in scope with regard to the type of compound to be administered.

The claims are very broad in scope with regard to the type of disease to be treated. The claims cover a wide variety of neurodegenerative diseases. As examples, the specification specifically mentions Alzheimer disease, Parkinson disease, the prion disorders, Huntington disease, dentatorubralpallidoluysian atrophy (DRPLA), and spinocerebellar ataxia type 1 and 3 (SCA1 and SCA3) (page 1, lines 15-20).

Furthermore, the claims are very broad in scope with regard to the type of therapeutic effect to be achieved by the method.

Amount of direction or guidance presented and the presence or absence of working examples. Example 5 of the specification reveals that ataxin-1 aggregates in SCA1 patients and a transgenic mouse model of ataxia are positive for HDJ-2/HSDJ (pages 20-21). The specification also discloses that ataxin-1 aggregation is suppressed following overexpression of HDJ-2/HSDJ in HeLa cells. The specification does not include any working examples of the claimed invention. Although the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation, it is a factor to be considered, especially in a case involving an unpredictable art such as the therapeutic arts. See MPEP 2164.02.

With regard to gene therapy the specification provides only limited and general guidance at page 5, lines 3-6 and page 14, lines 18-22. The teaching provided in the specification only states that the introducing step of the chaperone can be by gene therapy and that gene therapy modes of introduction can be used to target the introduction of the compound. The specification fails to provide any specific

guidance on the generation of the nucleic acid construct to be used in the gene therapy method, on the delivery methods of the nucleic acid, and on the targeting of neurological tissue.

State of the prior art and predictability of the art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely achievable by those skilled in the art. This is reflected in two reviews published around the priority date of this application. Verma et al. (1997) discloses that "there is still no single outcome that we can point to as a success story" (page 239, column 1). The authors go on to state "[t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, column 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, column 1) and concludes that "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (page 30). The instant specification fails to provide guidance to the skilled artisan on the parameters for gene delivery for the breadth of the claimed invention. Numerous factors complicate the gene delivery art which cannot be overcome by routine experimentation. These include the fate of the DNA vector itself (volume of distribution, rate of clearance in the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. Hodgson (1995) discusses the drawbacks of viral transduction and chemical transfection methods and states that "[d]eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pages 459-460). Miller et al. (1995) also review the types of vectors available for *in vivo* gene delivery and conclude that "for the long-term success as well as the widespread applicability of human gene

therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). In the instant application, the specification provides no teachings on the generation of the nucleic acid construct to be used in a gene therapy method, on the delivery method for the nucleic acid, nor on the targeting of neurological tissue. In the absence of specific guidance, the skilled artisan would have been required to develop successful protocols for practicing the claimed methods, without guidance on a starting point or the direction in which experimentation should proceed. However, given that the gene therapy art was considered highly unpredictable and undeveloped, the skilled artisan would have been required to engage in undue experimentation to come up with successful gene therapy protocols.

The claims encompass a wide variety of neurodegenerative diseases. Price et al. (1998) teaches that the "neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine" (abstract). The specification teaches that the term "neurodegenerative disorders" refers to those disorders which have the characteristic of insoluble aggregates in the cells of the nervous system (page 10, lines 9-12). However, not all neurodegenerative diseases or disorders have the histological characteristic of insoluble aggregates in the cells of the nervous system. See Kumar et al. at pages 725-729. The specification does not teach how a therapeutic effect would be achieved in a patient with a neurodegenerative disease or disorder that is not characterized by the deposition of insoluble protein aggregates in the neural tissue.

The claims encompass a wide variety of chaperones. However, given that the gene therapy art is highly unpredictable and further given that the specification fails to provide specific guidance on which nucleic acids encoding which chaperone can be used to treat a specific neurodegenerative disease of interest, the skilled artisan would have been required to engage in undue experimentation to develop a method within the scope of the claims for treating any particular neurodegenerative disease.

In an article published after the effective filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far ..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pp. 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of vector types to treat a wide variety of neurodegenerative diseases. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation.

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al., p. 1789, column 1, paragraph 1). Rather, the prior art shows that intensive investigation has met with limited success.

With regard to protein therapy and non-protein, non-nucleic acid compound therapy, the art emphasizes the difficulty associated with developing successful treatment protocols. As discussed above, Price et al. (1998) teaches that the "neurodegenerative disorders, a heterogeneous group of chronic

progressive diseases, are among the most puzzling and devastating illnesses in medicine" (abstract) and Kumar et al. (1992) discloses that "[u]nlike other categories of disease such as infections or trauma that may share etiological origins, the degenerative diseases are unified only by some general clinicopathologic features. Currently, almost all are of obscure origin, and there is no compelling reason to suppose that they have the same, or even a similar type of cause" (pages 725-726). A wide variety of therapeutic strategies for the treatment of neurodegenerative diseases are being pursued. However, despite intensive effort on the research front, the existence of successful treatment protocols was extremely limited in 1998.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Claims 24 and 25 are reach-through claims. The specification fails to disclose any particular structure for the full scope of the compounds recited in the claims, other than HDJ-2/HSDJ as noted above. The specification does not provide any guidance or working examples in this unpredictable art, and thus the artisan would have been unable to prepare the full scope of compounds recited in the claims. Furthermore, an assay for *finding* a product is not equivalent to a positive recitation of *how to make* a

product. These claims fail to meet the enablement requirement for the "how to make" prong of 35 U.S.C. 112, first paragraph.

Given the limited examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon *in vivo* administration of a compound as recited in the claims, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon administration of a compound as recited in the claims, undue experimentation would have been required for one skilled in the art to develop a protocol within the scope of the claims for treating a wide variety of neurodegenerative diseases.

At page 10, paragraph 3 of the response, Applicants assert that the amended claims use the terms "chaperone preparation" and "compound preparation." Applicants conclude that these terms do not cover gene therapy approaches because the cells or vectors introduced in gene therapy approaches do not constitute a preparation of either the compound or the chaperone. Contrary to Applicants belief, a nucleic acid is a compound and would ordinarily be prepared as a "compound preparation" by combining it with a pharmaceutically acceptable carrier for *in vivo* administration. Likewise, the term "chaperone preparation," when given its broadest reasonable interpretation, clearly covers a nucleic acid encoding a chaperone. Applicants are reminded that the original claims recite "introducing a therapeutic effective amount of a chaperone" (Claim 1) and "[t[he method of claim 1, wherein the introducing step includes introducing the chaperone or chaperone-like-compound into the mammal by gene therapy" (Claim 2). Thus, where the claims recite introducing a chaperone, the claim language is clearly intended to encompass introducing the chaperone indirectly by introducing a nucleic acid that encodes the chaperone (also see the specification at page 4, line 30 to page 5, line 6). Likewise, the term "chaperone preparation" can readily be interpreted to include a nucleic acid composition encoding the chaperone. If Applicants wish to now limit the claims so that they no longer encompass gene therapy, claim language reciting "administering a composition consisting essentially of a chaperone protein" would be remedial.

At page 11, paragraph 2 of the response, Applicants assert that chaperone proteins are well known in the art and therefore the claims are not overly broad in referring to chaperones. However, the issue is not whether chaperones are well known in the art or not, the issue is whether the specification enables the skilled artisan to select appropriate chaperones from this very large class of proteins that have the desired therapeutic activity. The problem is that the specification provides no guidance, beyond the use of HDJ-2/HSDJ in treating SCA1, as to which chaperones should be used to treat which diseases. The chaperones are a very large class of proteins and one of skill in the art would not be able to use routine experimentation to determine which chaperones are useful for treating Alzheimer's disease, which chaperones are useful for treating Parkinson's disease, which chaperones are useful for treating Huntington disease, etc. Given the very large number of diseases, the very large number of chaperones, and the unpredictability in the therapeutic arts, developing therapeutic protocols across the full scope of the claimed invention would require undue experimentation. Furthermore, the claims cover introducing compounds that are not chaperones. Applicants do not address this issue.

At page 11, paragraph 3 of the response, Applicants assert that the specification defines the term "neurodegenerative disorders" to encompass only those neurodegenerative disorders "which have the characteristic of insoluble aggregates in the cells of the nervous system." Nevertheless, it is maintained that the claims are very broad in scope with regard to the type of disease to be treated (see page 6, paragraph 1 of the Office Action mailed 10/22/03). The claims cover a wide variety of neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), prion disorders, Huntington disease, dentatorubralpallidoluysian atrophy (DRPLA), and spinocerebellar ataxia type 1 and 3 (SCA1 and SCA3).

At pages 12-14 of the response, Applicants present various post-filing references that allegedly support the enablement of the claimed invention. However, notably missing from each and every one of the 8 references cited is methodology for delivering exogenous protein into the Purkinje cells of the

cerebellum. The claims are directed to delivering large proteins to cerebellar cells, particularly Purkinje cells of the cerebellum. The art of record in this case, as well as the 8 post-filing references cited in this response, clearly teach that chaperone proteins carry out their function **intracellularly**. Thus, it is evident that, in order for the exogenously delivered chaperone proteins to function to suppress ataxin-1 aggregation or protein aggregation in general, the chaperone proteins must be taken up into the appropriate cells, i.e. the cells where the aggregation is occurring. The specification teaches that in the case of SCA-1, ataxin-1 aggregation occurs in the Purkinje cells of the cerebellum. Thus, the exogenous chaperone proteins must be delivered across the blood brain barrier to reach the brain tissue. However, since chaperones function intracellularly, the exogenous, now interstitial protein, must be taken up by the affected neurons (i.e., the Purkinje cells). Neither the specification, nor the prior art teaches how to accomplish this. The examples of the specification rely on *in vivo* expression of the chaperone protein by using transgenic mice that contain a transgene encoding the relevant chaperone protein. This obviates the very difficult task of *in vivo* protein **delivery**. However, the protein delivery problem remains unsolved to the present day. None of the post-filing references demonstrate *in vivo* protein delivery to the CNS with cellular uptake of the administered protein. Where the post-filing references describe *in vivo* experiments, the investigators relied on expression and overexpression of the proteins being studied. They did not deliver exogenous protein to the brain. One obstacle to protein delivery to the CNS is the blood brain barrier, which is well known in the art to permit only the passage of very limited types of molecules (see Emerich (2000) Exp. Opin. Ther. Patents 10(3): 279-287). Through this very effective, selectively permeable barrier, the internal chemical environment of the brain is maintained at a very precise composition.

The specification contemplates various routes of administration for the agent, including oral administration, parenteral injection, rapid infusion, nasopharyngeal absorption, and dermoabsorption. The specification further contemplates intramuscular, intravenous, and suppository administration of the

agent (page 14, lines 10-18). None of these modes of delivery can be used to deliver proteins into the brain and into the interior of Purkinje cells. While proteins can be administered to the brain through surgical means, implantation of a controlled-release microcapsule, and stereotactic injection, such methods would only deliver the protein to the brain tissue and would not result in cellular uptake. For the reasons discussed above, chaperone proteins carry out their functions intracellularly, generally in the cytoplasm of the cells where proteins are being synthesized. Extracellular delivery within the brain tissue will not be useful because chaperones cannot carry out their function extracellularly, and methods for achieving cellular uptake of extracellular proteins by Purkinje cells of the cerebellum have not been developed. The specification provides no guidance on the delivery of exogenous protein to target cells in the brain. Further, Emerich (2000) discloses that limited modes of delivery were known in the art for drug delivery to the brain. None of these delivery methods result in cellular uptake of large protein molecules. Dietz and Bahr (2004) disclose sophisticated means for delivery of bioactive molecules **into the cell**. However, as of the effective filing date of this application (May 1998), the *in vivo* delivery of large proteins into the cytoplasm of Purkinje cells had not been achieved.

At page 14 of the response, Applicants assert that the animal model and *in vitro* model studies are sufficient to provide enablement for methods performed in humans when there is adequate correlation. Contrary to Applicants assertion, *in vivo* protein delivery methods into target cells of the brain or enabled gene therapy protocols are required to carry out the claimed method. Applicants assert that animal and *in vitro* models should be accepted as correlating unless the Examiner has evidence that the model does not correlate. In the instant case, the Examiner has provided ample evidence that the models do not correlate because the model systems used obviate the most problematic obstacle of the invention, which is *in vivo* delivery of the agent to target cells of the brain. *In vitro* models (i.e. cell culture systems) do not have the higher order tissue structure and organ structure of a multicellular organism. However, even in the cell culture systems genetic modification was used instead of direct protein delivery. In other words, the cells

were not contacted with the chaperone protein and faced with the challenge of cellular uptake. Likewise, the transgenic models relied on genetic modification of the animal to get the chaperone expressed within the Purkinje cells. *In vivo* protein delivery to Purkinje cells of the cerebellum was not attempted. For the reasons discussed above and in the prior Office Action, undue experimentation would be required to carry out the claimed method, even in a single embodiment, let alone the full scope.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER